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Jerome B. Zeldis

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Jones Day
222 East 41st Street
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EXAMINER

SZNAIDMAN, MARCOS L

ART UNIT

PAPER NUMBER

1612

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/534,324	Applicant(s) ZELDIS, JEROME B.	
	Examiner MARCOS SZNAIDMAN	Art Unit 1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 September 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3,5-9,11,15,22,41-47,50 and 51 is/are pending in the application.
- 4a) Of the above claim(s) 50 and 51 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3,5-9,11,15,22 and 41-47 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>2 pages 08/30/09</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This office action is in response to applicant's request for continued examination filed on September 23, 2009.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendments to the claims filed on July 8, 2009 had already been entered in the Advisory Action filed on July 22, 2009.

Status of Claims

Claims 1, 3, 5-9, 11, 15, 22, 41-47 and 50-51 are currently pending and are the subject of this office action.

Claims 50 and 51 were withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention/species, there being no allowable generic or linking claim.

Claims 1, 3, 5-9, 11, 15, 22 and 41-47 are presently under examination.

The following species are currently under examination:

hydroxyurea as the second active agent, which was elected by Applicant in the reply filed on July 23, 2008.

Priority

The present application is a 371 of PCT/US03/11325 filed on 04/13/2003, and claims priority to provisional application No. 60/424,731 filed on 11/06/02.

Information Disclosure Statement

The Information Disclosure Statement filed on August 30, 2009 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. A signed copy of the IDS is attached hereto.

Rejections and/or Objections and Response to Arguments

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated (Maintained Rejections and/or Objections) or newly applied (New Rejections and/or Objections, Necessitated by Amendment or New Rejections and/or Objections not Necessitated by Amendment). They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1) Claims 1, 5, 15, 22 and 41-47 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Tsimberidou et. al. (Cancer Chemotherapy and Pharmacology (2002) 50:237-242, cited in previous office action) in view of Man et. al. (WO 2001/34606, cited in previous office action).

Claims 1 and 41 recite a method for treating, managing or increasing the therapeutic efficacy of a myeloproliferative disease, which comprises administering to a patient in need of such a treatment a therapeutically effective amount of

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cyclopropanecarboxylic acid {2-[(1S)-1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1H-indol-4yl}-amide or a pharmaceutically acceptable salt (from now on compound A, see structure in claim 41), wherein the myeloproliferative disease is selected from the group consisting of: agnogenic myeloid metaplasia among others, and wherein the therapeutically or prophylactically amount is from about 5 mg to about 50 mg per day.

Claim 44, further limits claim 1, wherein the compound is administered in an amount of about 10 mg, 20 mg, about 25 mg or about 50 mg per day.

Claim 45, further limits claim 1, wherein the compound is administered in an amount of about 10 mg to about 25 mg per day.

Claim 46 further limits claim 1, wherein the compound is administered in an amount of about 20 mg per day.

For claims 1, 41 and 44-46, Tsimberidou teaches a method of treating agnogenic myeloid metaplasia (AMM, a myeloproliferative disease) with Etanercept (an inhibitor of the cytokine Tumor necrosis factor-alpha (TNF-alpha)) (see abstract). In particular, the reference teaches that signs of clinical improvement were noted in some patients, particularly in those with AMM (see page 240, lines 3-5) and they give further experimental data that corroborate these results (see third and fourth paragraph on page 240). Tsimberidou further teaches that TNF-alpha is a major effector and regulatory cytokine involved in the pathophysiology of myeloproliferative disorders, including, among others: agnogenic myeloid metaplasia (AMM) (see introduction on page 237, first three lines). Therapeutic strategies targeting TNF-alpha include: 1-

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soluble TNF receptors, which inactivate TNF-alpha; 2- anti-TNF-alpha monoclonal antibodies, and 3- agents modulating TNF-alpha signaling (see page 237 under Introduction, second paragraph). In other words, Tsimberidou teaches that compounds that inhibit the action of TNF-alpha, either by binding to TNF-alpha directly, like Etanercept or monoclonal antibodies, or by preventing its formation (i.e. agents modulating TNF-alpha signaling like for example decreasing the levels of TNF-alpha like thalidomide (see page 240, left column, third paragraph)), are equivalent in terms of treating diseases wherein the activity of the TNF receptors has to be decreased.

Tsimberidou et. al. do not teach the treatment of AMM or any myeloproliferative disease with compound A in an amount of 5 mg to about 50 mg per day or the amounts recited in claims 44-46. However, Man teaches that compound A (see page 67, Example 57) belongs to a class of compounds that are non-polypeptide isoindoline derivatives that decrease the levels of TNF-alpha (see page 1, lines 6-7). The compounds can be used under the supervision of a qualified professional, to inhibit undesirable effects of TNF-alpha (see page 22, lines 1-3).

Man further teaches that inhibition of TNF-alpha by these compounds can be conveniently assayed using methods known in the art (see page 20, lines 6-9). It further teaches that dosage regimens must be titrated to the particular indication, the age, weight, and general physical condition of the patient, and the response desired but generally doses will be from about 1 to about 1,000 mg/day as needed in single or multiple daily administrations. In general, an initial treatment regimen can be copied from that known to be effective in interfering with TNF-alpha activity for other TNF-alpha

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mediated disease states by the compounds of the present invention (see page 22, lines 12-18).

Since Tsimberidou teaches a method of treating AMM with compounds like Etanercept or Thalidomide that decrease the activity of the TNF receptor, and since Man teaches that compound A is a compound that decreases the activity of the TNF receptor, at the time of the invention it would have been *prima facie* obvious for a person of ordinary skill in the art to substitute one functional equivalence (Etanercept, Thalidomide, or any compound that decreases the activity of the TNF receptor) for another (compound A) with an expectation of success, since the prior art establishes that both function in similar manner.

Further, knowing the amount of inhibitory effect of compound A against TNF-alpha, and knowing the dosages recommended by Man (1 to about 1,000 mg/day) and the suggestion that the initial dosage can be copied from other TNF-alpha related diseases (like AMM), the skilled in the art will be able to optimize the dose of compound A required to effectively treat AMM, since dose optimization for these type of diseases is routine practice in the pharmaceutical art as stated by Man, thus resulting in the practice of claim 1, 41 and 44-46 with a reasonable expectation of success.

Claim 5 further limits claim 1, wherein the patient is refractory to conventional myeloproliferative disease treatment.

For claim 5, Tsimberidou further teaches that patients that had refractory AMM can also be treated with TNF-alpha inhibitors (see page 238, under study groups).

Claim 15 further limits claim 1, wherein compound A is enantiomerically pure.

For claim 15, Man teaches the enantiomerically pure form of compound A (S enantiomer, see page 67, Example 57).

Claim 22 further limits claim 1, wherein the administration of Compound A occurs before, during or after transplanting: umbilical cord blood, placental blood, peripheral blood stem cell, hematopoietic stem cell preparation or bone marrow in the patient.

For claim 22 Tsimberidou further teaches that AMM can be further treated with stem cell transplantation (see page 240, left column, beginning of third paragraph).

At the time of the invention it would have been *prima facie* obvious for a person of ordinary skill in the art to treat AMM combining two methods (administering a compound that decreases the activity of TNF-alpha like compound A, and transplanting stem cells) each of which is taught by the prior art to be useful for the same purpose (treating AMM), in order to form a third method to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art (see MPEP 2144.06). *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). Further, since the administration of compound A can only occur before, during or after the stem cell transplantation, this would result in the practice of claim 22 with a reasonable expectation of success.

Claim 42 further limits claim 1, wherein compound A is administered orally.

Claim 43 further limits claim 43, wherein the compound is administered in the form of a capsule or tablet.

For claims 42 and 43, Man further teaches that compound A can be administered orally in the form capsules and tablets (see page 22, lines 3-7).

Claim 47, further limits claim 1, wherein compound A is a pharmaceutically acceptable salt.

For claim 47, Man further teaches salts of the compounds of the invention including compound A (see page 12, lines 13-19).

2) Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tsimberidou et. al. (Cancer Chemotherapy and Pharmacology (2002) 50:237-242, cited in previous office action) in view of Man et. al. (WO 2001/34606, cited in previous office action) as applied to claims 1, 5, 15, 22 and 41-47, further as evidenced by Canepa (British Journal of Haematology (2001) 115:313-315, cited in prior office action).

Claim 11, further limits claim 1, wherein the myeloproliferative disease is primary or secondary.

Tsimberidou and Man teach all the limitations of claim 11, except for the myeloproliferative disease being primary or secondary. However AMM is a primary myeloproliferative disease as evidenced by Canepa. Canepa teaches that aMMM (i.e. agnogenic or idiopathic myelofibrosis, AMM) is a primary as opposed to a secondary type of myelofibrosis (see abstract).

3) Claim 3 and 7-9 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Tsimberidou et. al. (Cancer Chemotherapy and Pharmacology (2002) 50:237-242, cited in prior office action) In view of Man et. al. (WO 2001/34606, cited in prior office action) as applied to claims 1, 5, 15, 22 and 41-47 above, and further in view of Alter et. al. (Blood (1985) 66:373-379, cited in prior office action).

Claims 3 and 7-9 further limit claim 1, wherein a second active agent (claim 3) is used with compound A in order to treat a myeloproliferative disorder, wherein the active agent is capable of suppressing the overproduction of hematopoietic stem cells or ameliorating one or more of the symptoms of the myeloproliferative disease (see claim 7) and wherein the second active agent is hydroxyurea (species elected, see claims 8 and 9).

Tsimberidou et. al. and view of Man et. al. teach all the limitations of claims 3 and 7-9, except for using hydroxyurea for the treatment of AMM (a myeloproliferative disorder). However, Alter et. al. teach that hydroxyurea is an effective treatment for AMM (see abstract and Table 1 on page 374).

At the time of the invention it would have been *prima facie* obvious for a person of ordinary skill in the art to treat AMM combining two compositions (compound A and hydroxyurea) each of which is taught by the prior art to be useful for the same purpose (treat AMM), in order to form a third composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art (see MPEP 2144.06). *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ

1069, 1072 (CCPA 1980). All this would result in the practice of claims 3 and 7-9 with a reasonable expectation of success.

4) Claim 6 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Tsimberidou et. al. (Cancer Chemotherapy and Pharmacology (2002) 50:237-242, cited in prior office action) In view of Man et. al. (WO 2001/34606, cited in prior office action) as applied to claims 1, 5, 15, 22 and 41-47 above, and further in view of Canepa et. al. (British Journal of Haematology (2001) 115:313-315, cited in prior office action).

Claim 6 further limits claim 5, wherein the patient is refractory to a myeloproliferative disease treatment comprising thalidomide.

For claim 6, and as mentioned before, Tsimberidou teaches that patients with refractory AMM or any other myeloproliferative disease can be treated with a compound that decreases the activity of the TNF receptor (i.e. Etanercept or compound A, see page 238 under study group).

Tsimberidou in view of Man teach all the limitations of claim 6, except when the patient is refractory to a myeloproliferative treatment that comprises thalidomide. However, Canepa teaches that thalidomide has been used effectively for the treatment of myeloproliferative diseases (i.e. thalidomide is a conventional treatment of myeloproliferative diseases, see title and abstract).

Since Tsimberidou in view of Man teach that patients that had refractory AMM can also be treated with TNF-alpha inhibitors like compound A, at the time of the invention, it would have been *prima facie* obvious for the skilled in the art to treat a

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patient that is refractory to any myeloproliferative disease treatment, like treatment with thalidomide as taught by Canepa, thus resulting in the practice of claim 6 with a reasonable expectation of success.

Response to Applicant's arguments related to the above rejection

Applicant's arguments have been fully considered but are not persuasive.

Applicant argues that: The Examiner alleged that even though the modes of action of Etanercept and Compound A are different, the end result is allegedly the same because both allegedly decrease the activity of TNF alpha, either by directly binding to it (Etanercept) or by decreasing the amount of TNF-alpha in circulation (Compound A).

See the continuation sheet of the Advisory Action dated July 22, 2009.

The Applicant respectfully disagrees with the Examiner's allegation above because in order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on the mere fact that the components at issue are functional equivalents. In re Scott, 323 F.2d 1016, 139 USPQ 297 (CCPA 1963). Here, the examiner has not provided evidence to show that the equivalency of the two modes of action (i.e., **action of binding of TNF-alpha** is equivalent to the **action of decreasing the levels of TNF-alpha**) has been recognized in the prior art. Actually, the Examiner has admitted that the two modes of action are different, and therefore not equivalent. See line 4 of the continuation sheet of the Advisory Action dated July 22, 2009. Because the two modes of action are different, the Applicant respectfully submits that the Examiner's allegation

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is merely based on the alleged fact that the two modes of action at issue are functional equivalents, i.e., providing the same "end result", without evidence showing that the equivalency of the two modes of action has been recognized in the prior art. Such reliance on equivalence as a rationale to support an obviousness rejection by the Examiner is expressly and legally prohibited under *In re Scott*.

Examiner's response:

As discussed in the above rejection, Tsimberidou teaches that therapeutic strategies targeting TNF-alpha include: 1- soluble TNF receptors, which inactivate TNF-alpha; 2- anti-TNF-alpha monoclonal antibodies, and 3- agents modulating TNF-alpha signaling (see page 237 under Introduction, second paragraph). In other words, Tsimberidou teaches that compounds that inhibit the action of TNF-alpha, either by **binding to TNF-alpha** directly, like **Etanercept** or monoclonal antibodies; or by preventing its formation (i.e. agents modulating TNF-alpha signaling like for example **decreasing the levels of TNF-alpha** like **thalidomide** (see page 240, left column, third paragraph, see also reference 23 by Gutschow et. al.)) are equivalent in terms of treating diseases wherein the activity of the TNF receptors has to be decreased. In other words, although the mechanism of action of Etanercept and Thalidomide are different, the end result is the same: **the reduction of free (i.e. unbound) TNF-alpha available** in the system, in one case because Etanercept binds directly to the TNF-alpha, and in the other one, because Thalidomide, like compound A, simply decreases the levels of free TNF-alpha available; and as a consequence, both are known to effectively treat AMM.

Based on the above teachings, the skilled in the art will recognize that **Etanercept, Thalidomide and compound A are equivalents** because they all **reduce the amount of free (unbound) TNF-alpha**, which according to Tsimberidou is key to the treatment of AMM (see page 237, Introduction), regardless of their mechanism of action.

Finally, Tsimberidou refers to Gutschow (Bioorganic and Medicinal Chemistry (2001) 9:1059-1065, reference 23, included just for evidentiary purposes and as part of the rejection itself) when referring to agents that modulate TNF-alpha signaling. Gutschow teaches that Thalidomide is a selective inhibitor of TNF-alpha production (i.e. **decreases the levels of TNF-alpha**, see page 1059, under Introduction, left column, lines 6-11).

Conclusion

No claims are allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is

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(571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCOS SZNAIDMAN/
Examiner, Art Unit 1612
November 23, 2009.